

**An Assessment of Implications of Adaptive Licensing
for Pharmaceutical Intellectual Property and
Regulatory Exclusivity Rights in EU**

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Introduction

One of the key advantages of adaptive licensing is to align the licensing of new medicines more closely with patient needs for earlier access to beneficial treatments. From an innovators perspective 'earlier' market access may seem an obvious incentive to gain earlier revenue generation. This is however, offset with an 'earlier' start to patent protection periods- which depending on the technology, disease, population and timing of subsequent asset protection periods, can present a conflict.

Adaptive licensing and Adaptive pathways

The term 'adaptive licensing' (AL) was originally coined to describe, "a prospectively planned, flexible approach to regulation of drugs and biologics, through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation".¹ With this regard, the term "license" is used interchangeable with the term "market authorization" or "approval". Later on, this approach was broadened to 'adaptive pathways' to integrate key elements of clinical drug development, licensing, reimbursement and coverage, utilization in clinical practice, and monitoring of treatment outcomes.²

From a licensing perspective, adaptive concepts center on utilizing existing legislative tools such that the applicable technology could receive an 'initial' marketing authorization (MA) in a targeted sub population (limited indication) via a full MA, or under a MA linked with conditions (conditional, or under exceptional circumstances). Under European Medicines Agency (EMA) guidelines, a conditional MA is granted under the conditions that it fulfills an unmet medical need, based on less comprehensive data than normally required, but on the provision that the applicant should be in a position to provide comprehensive clinical data in the future.³ However,

the authorisation of medicinal products for an initially restricted sub-population, or under a conditional MA, will have consequences for other relevant aspects of the product development, such as the application of the different protection schemes that exist for innovative medicines.

It will therefore be key to understand firstly, the role of the MA as well as its impact on existing exclusivity rights and periods in case of an authorization within the conceptual model of adaptive pathways and secondly, in particular on the calculation of the regulatory data protection (RDP) and supplementary protection certificate (SPC) periods. Thirdly, the area of orphan product designation - products intended for the treatment of life-threatening or very serious diseases that are rare (such as some cancers, genetic or autoimmune conditions) benefit from an orphan market exclusivity (OME) right, based on their respective designation, which is different from non-orphan products. All these areas are relevant as an earlier licensing could, amongst other things, lead to an erosion of protection periods in subsequent indications throughout the lifecycle of the product.

Does the existing intellectual property (IP) and regulatory exclusivity right framework have the capacity to support these new Research & Development (R&D) models under adaptive pathways and adaptive licensing? If not, what new considerations are warranted?

In this article we focus on the current EU legislative framework for intellectual property (IP) and regulatory exclusivity rights, their respective roles, how they are linked to MAs and supplementary protection periods, and which issues may arise under an adaptive pathway. We highlight several case studies that bring to the fore some of the key issues at hand and learnings that have the potential to inform both adaptive licensing

and adaptive pathways, and further considerations within the context of the EU legal framework.

1. Role of Exclusivity Rights

The research and development of new medicines is not only a long, but also a costly process.⁴ Out of thousands of compounds being tested only very few make it to market. This hugely expensive undertaking requires appropriate protection of the process and the assets it produces. Investors take substantial risks when deciding to develop new or improve existing drugs, as there is no certainty that this undertaking will be successful. In order to recoup related costs and allow for a return on investment, an adequate protection by exclusivity rights for a limited and legally defined period of time, is therefore fundamental in the pharmaceuticals industry. Exclusivity rights are the key incentives for the innovator to continue to take the risk and invest in developing new medicines, while the “old” medicine can be copied (through generic or biosimilar pathways) after expiry of the exclusivity rights.⁵

The key exclusivity rights cover two main areas. They are on the one side **IP rights**, in particular patents. **Patents** are exclusive rights granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention. Although the procedure for granting patents and the scope of the exclusive rights vary between the regions and countries, a granted patent typically includes one or more claims that define the invention, and these claims must meet relevant patentability requirements, such as novelty, usefulness, and non-obviousness. The patent exclusivity right consists of the right to prevent others from making, using, selling, importing, or distributing a patented invention without permission of the patent holder for a limited period of time. The protection for

medicines may in particular refer to the compound itself, its uses and pharmaceutical forms, as well as to the manufacturing process.⁶

As the time between patent filing and authorisation of medicinal products has increased substantially over time, and by this mechanism the effective period of patent protection decreased, some legislators foresaw a prolongation of the patent protection in order to cover the investment put into the research. For this reason, in 1992 the EU legislator introduced the **Supplementary Protection Certificate (“SPC”)** for medicinal products.⁷

On the other side, which is especially true for the EU, **regulatory exclusivity rights** become ever more important for the protection of medicines against being copied. This is in particular the case for “old” molecules for which a patent protection has meanwhile expired, or for biological medicines that do not benefit from a single compound patent. The background for regulatory exclusivity rights is that, as a rule, no medicinal product may be placed on the market before the quality, safety and efficacy of the product has been assessed and approved by the competent authorities in a MA procedure. To obtain such a necessary MA, extensive data, including nonclinical and clinical research data, have to be provided in order to demonstrate the quality, safety and efficacy of the medicinal product under evaluation. As this requires a significant amount of time, resources and money, a lot of countries, in particular those being party of the Trade Related Aspects of Intellectual Property Rights (TRIPS)-Agreement,⁸ meanwhile recognized the necessity to offer proper protection of these nonclinical and clinical data for a limited duration of time in the form of the so-called **Regulatory Data Protection (“RDP”)**, to enable adequate recovery of and return on investment for the costs of these research requirements.⁹ This RDP may exist of a so-called **data exclusivity (DE)** period during which i) the data submitted may not be relied upon by

third parties and/or will not be accepted by the responsible Health Authority (HA) for another MA application, and/or such ii) a MA will not be granted by the responsible HA and/or a period of **market protection (MP)** during which a MA, relying on such data, may not be placed on the market.

Over the last decades, not only has the extension of RDP periods been introduced to stimulate new research in specific areas, but in some countries also a special exclusivity right has been introduced as a reward to bringing to the market medicines for patients suffering from rare (orphan) diseases, the so-called **Orphan Market Exclusivity (“OME”)**. In the EU, OME prevents the coming to the market of similar products for the same indication for a period of ten years.

In general, these regulatory exclusivities are without prejudice to existing IP rights¹⁰ and also differ in scope and content of protection between the countries. With respects to RDP, for example, in the EU there exists a combination of 8 year DE and additional 2 year of ME (see more detailed in section 2c), in the US for new chemical entity small molecules a 5 year DE and for biologics a 12 year DE period, Switzerland provides 10 year of DE, Canada 6 years DE and additional 2 years of MP, Russia and Turkey has 6 years of DE, while Australia, New Zealand and Malaysia have just 5 years of DE.¹¹

As it becomes obvious, regulatory exclusivity rights differ widely from IP rights: Patents and SPCs protect inventions and provide the patent holder with a legal monopoly with regard to the subject of the patent, e.g. the active substance of a medicinal product, in a way that it protects against placing on the market of products with the same active substance by other companies for the duration of the patent protection, eventually prolonged by SPC. RDP, however, rewards the effort of having performed extensive non-clinical and clinical tests for getting a medicinal product authorised in a way that other companies may not refer to it in order to get their own MA or have to wait a

certain period before they can place a generic or biosimilar medicinal product on the market.¹²

In order to also stimulate development and accessibility of medicinal products for use in the paediatric population specifically, (paediatric-specific versions of medicinal products may be required due to different pharmacokinetics and pharmacodynamics compared to adults) additional rewards were introduced for the conduct of such activities prolonging existing exclusivity rights (so-called “**paediatric rewards**”).¹³

2. Current Landscape of IP and Regulatory Exclusivity Rights in the EU

The EU provides all of the above mentioned IP rights and regulatory exclusivity rights in order to foster innovation and development of medicinal products in general as well as in particular for the areas of orphan diseases and treatment of paediatric population. The current landscape looks essentially as follows:

a) Patent

The legal basis for patents in the EU is included in a number of EU regulations and directives as well as national patent laws. The European patent law is strongly shaped by international agreements¹⁴ and covers those legislations which are party to the European Patent Convention (EPC). For certain states in Eastern Europe, the Eurasian Patent Convention applies.

Patents in the EU still have an effect only with regard to the territory of the Member State. Today, in those countries being a member of the EPC, patents are still either granted nationally by the national patent offices, or through a centralised patent prosecution process at the European Patent Office (EPO).¹⁵ A patent granted by the EPO, however, does not lead to a single European patent enforceable before one single court, but rather to a bundle of essentially independent national European

patents enforceable before national courts according to different national legislations and procedures. Similarly, Eurasian patents are granted by the Eurasian Patent Office and become, after grant independent national Eurasian patents, enforceable before national courts. The validity of the patent is usually 20 years after the filing of the patent application.

The basis for the creation of a **unitary patent** with EU-wide effect was put into place via respective EU regulations¹⁶, but will only apply once the related Agreement on a Unified Patent Court enters into force.¹⁷ A patent granted for a medicinal product does not have any link and is independent of the grant of the MA for this specific product.

b) Supplementary Protection Certification (SPC)

As already briefly stated above, the SPC was created and introduced in 1992 by a respective EU-Regulation in order to encourage innovation by compensating for the long time (average of 8-10 years) needed to obtain regulatory approval of medicinal products. After several substantial amendments, this regulation got codified by a new regulation in 2009, namely by Regulation (EC) No 469/2009.¹⁸

By its nature, the SPC as an IP right provides an extension of the duration of certain rights associated with a basic patent¹⁹ by a maximum of 5 years²⁰, whereas the total combined duration of exclusivity of such a basic patent and SPC cannot exceed 15 years starting with initial approval of the medicinal product.²¹ A SPC can therefore only be granted if the approval takes place later than 5 years after the start of the basic patent protection. Due to the fact that patents are granted country-by-country, applications for SPC also have to be filed and approved on a country-by-country basis.²²

c) Regulatory Data Protection

The Regulatory Data Protection (RDP) is laid down in Article 10(1) of Directive 2001/83 for nationally²³ and in Article 14(11) of Regulation 726/2004 for centrally approved MAs. The objective is to provide protection for the data package of an authorised medicinal product for a defined period of time in situations where a second applicant wishes to refer to the data included in a dossier of an innovator product (the reference medicinal product) or the reference medicinal product as such for the purpose of obtaining a respective generic or biosimilar MA.

The scope of RDP is therefore the protection of the results of preclinical tests and clinical trials of the reference medicinal product concerned, for which the default application is a full application containing all required documents and particulars.²⁴ However, to prevent the unnecessary testing of medicinal products in humans and animals as well as to save resources, Article 10 of Directive 2001/83 provides for several so-called 'abridged procedures' which exempt the second applicant - in part or in full - from providing results of its own nonclinical and clinical tests, but allow third persons to refer to innovators' data in the MA dossier of the same or a similar reference medicinal product (<see figure 1>).²⁵

Due to this, the current RDP rules laid down in Article 10(1) of Directive 2001/83 and Article 14(11) of Regulation 726/2004 provide for an 8 year DE period starting with initial MA grant during which a medicinal product may not be used as a reference medicinal product for the purposes of an abridged application procedure, and an additional 2 year MP period during which medicinal products authorised under these abridged procedure may not be placed on the market.²⁶ This 10 year RDP period can be prolonged by an additional year of market protection to a total period of 11 years (8+2+1 rule) under the condition that during the first 8-year period after initial MA grant a new therapeutic indication is authorised for this medicinal product which is held to

bring a significant clinical benefit in comparison with existing therapies.^{27, 28} A similar approach exists in the US where there is a 5 year period of new chemical exclusivity DE for small molecules that can be supplemented by additional 3 year periods of DE, which run concurrently, for new clinical investigations that may result in new formulations, indications, dosing regimens or over-the-counter (OTC) switches for the respective product (a prescription drug that is subsequently made available over-the-counter), and a 12 year period of data exclusivity for Biologic License Applications²⁹.

d) Orphan Market Exclusivity

Orphan Regulation 141/2000³⁰ introduced specific rules for orphan medicinal products with the main objective to stimulate research, development and authorisation of medicinal products for the treatment of patients suffering from rare conditions. This was mainly done by offering a special regulatory reward to companies that succeed in obtaining MA for such orphan products and by this bring such treatments to the market. The rationale is that certain conditions are so rare that the cost of developing and bringing to the market of a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the product and that, under normal market conditions, a pharmaceutical company would be unwilling to develop such a product. Therefore, where a medicinal product fulfils the criteria in Article 3 of the Orphan Regulation for being designated as an orphan medicinal product, Article 8(1) provides that upon authorisation the designated orphan medicinal product is entitled to a ten year period of OME during which competent authorisation shall not accept a MA application or grant a MA for a similar medicinal product for the same indication.

As the OME is linked with the approval of the product in the respective orphan indication, it runs concurrently with the RDP periods as far as it concerns its initial approval. On the one hand, OME offers a stronger protection than RDP as it provides

for a monopoly which blocks the coming to the market not only of product having the same active substance, but even of all “similar” products for a period of ten years. On the other hand, its scope is more limited than RDP as it does not refer to the substance as such, but only offers protection against products being similar and having the same (orphan) indication. Furthermore, OME rights can be derogated in the situations mentioned in Article 8(3) of the Orphan Regulation, i.e. where the sponsor of the orphan medicinal product has given consent to the second applicant, is unable to provide sufficient quantities of the orphan product, or where a second applicant can establish that the new product is safer, more effective or otherwise clinically superior to the orphan product.

e) Additional Rewards under the Paediatric Regulation

Under the Paediatric Regulation 1901/2006, the EU legislator introduced new rules to facilitate the development and accessibility of medicinal products for use in the paediatric population. In order to be able to file a MA application for a specific medicinal product, this Regulation obliges pharmaceutical companies as a rule to generate data for the intended use of this medicinal product in paediatric population in the form of a paediatric investigation plan (“PIP”).³¹ The PIP obligation not only applies to MA applications for new medicinal products but also to applications for the authorisation of new indications, new pharmaceutical forms and new routes of administration with regard to medicinal products which are protected either by a SPC or by a patent which qualifies for the granting of an SPC.³²

For the fulfilment of these PIP obligations, the Paediatric Regulation offers a prolongation of existing exclusivity rights, depending on the nature of the medicinal product in question: If an application contains all the results of research conducted in accordance with such an agreed PIP for a non-orphan product, Article 36(1) of the

Paediatric Regulation provides for a reward in the form of an six months extension of the SPC, irrespective of whether the completion of the PIP leads to the authorisation of a new paediatric indication or not.³³ For an orphan designated medicinal product a 6 month SPC extension cannot be obtained, as a special reward for orphan designated products is provided in Article 37 of the Paediatric Regulation in the form of a two-year extension of the orphan market exclusivity period.³⁴

3. Role of the Marketing Authorization for IP and Regulatory Exclusivity Rights

The MA is of utmost importance for the above-mentioned exclusivity rights as in the case in point in time of the (first) MA being granted defines the start of the duration of the respective exclusivity right. In those cases, the point in time of the MA grant is the trigger point for the “exclusivity clock”.

With respect to the IP rights, the MA is not relevant for the duration of a patent protection. However, the point in time of MA granting is decisive for the duration of a **SPC protection**, and by the same definition, also for a potential paediatric 6 month SPC extension: As laid out above, the SPC provides an extension of the duration of basic patents by a maximum of 5 years, whereas the total combined duration of exclusivity of such a basic patent and SPC cannot exceed 15 years starting with the *initial approval* of the medicinal product. As a consequence, with an initial approval of the product protected by a basic patent - assuming this is later than 5 years after start of the patent protection - the SPC clock starts running (see case study 1).

Case study 1: The question arose under which scenario the granting of a MA in one of the EU Member States, but also in another country (non EU member state), could be considered as being a first MA for the calculation of the SPC duration. This question was relevant for Switzerland: Even though Switzerland is not part of

the European Economic Area (EEA), a MA granted in Switzerland was automatically effective in Liechtenstein, which has been a member of the EEA since 1 May 1995. The European Court of Justice (ECJ) confirmed in case C-617/12 (*AstraZeneca AB v Comptroller General of Patents, Designs and Trade Marks*) that the MA granted in Switzerland was considered to be the first MA due to its immediate effect in Liechtenstein as an EEA member. This was the case although the data that persuaded Swissmedic to grant the (earlier) Swiss MA was held by the EMA to not be complete or persuasive enough to justify the grant of a MA under EU legislation. As a response to this ECJ decision, the contract between Switzerland and Liechtenstein was amended. Since 1 July 2005 the automatic effect of a Swiss MA in Liechtenstein is abolished. The recognition is now delayed by a time period, which is typically 12 months.

The same concept, as highlighted in case study 1 (i.e. the start of SPC period), also applies with regard to **RDP periods**, where the point of initial MA granting in the EU defines the start of the 10 year RDP period. This is an important concept effecting downstream exclusivity consideration and requires greater scrutiny with upstream planning (i.e. loss-of-exclusivity considerations) of adaptive licensing within adaptive pathways, as further discussed in section 4.

Due to the so-called “**Global Marketing Authorisation**” (GMA) principle, laid down in Article 6(1) of Directive 2001/83/EC³⁵, once a medicinal product has received an initial MA, any further product developments such as new indications, strengths, pharmaceutical forms and different presentations of existing medicinal products are considered to belong to the GMA of the initial product and will not lead to new or separate RDP periods. The consequence of the GMA is that all these product

developments will have the same RDP period as that of the original initial product (i.e. maximum of 10 years from the data of the initial MA).

In principle the point at which a MA is granted also defines the starting point for the 10 year **OME period**. However, the GMA principle does not apply to OME periods as it does to RDP: The OME right is linked to a specific therapeutic indication and not the compound. Therefore, it is possible that the same orphan medicinal product benefits from several periods of OME, each protecting a different indication, provided that these indications have separate orphan designations. Hence, if the newly authorised therapeutic indication falls within an orphan condition under which the product already got authorised, no new OME will be granted. If the newly authorised indication belongs to a new designated orphan condition, a new and independent OME period will apply (<see figure 2>).³⁶

In this context, it is important to understand that the **term “MA”** does not only include the full approval in accordance with Article 8 (3) of Directive 2001/83/EC, but all MAs that authorise the commercialisation of this product. This includes therefore also the conditional MA³⁷, the MA under exceptional circumstances³⁸ as well as the MA subject to conditions³⁹. However, necessary regulatory approvals for making available a medicinal product in the context of a compassionate use program⁴⁰ or named patient supply⁴¹ is not equal to and/or cannot be considered a MA as these are exemptions to the MA requirement rule, and therefore do not trigger the clock for any of the above mentioned exclusivity rights.

4. Implications of Adaptive Licensing on Exclusivity Rights

The adaptive pathways concept of the EMA, in order to achieve timely access for patients to potentially beneficial treatments, is based on the following three key principles:⁴²

- **iterative development**, which means either (1) **approval in stages**, beginning with a restricted patient population then expanding to wider patient populations, or (2) confirming the benefit-risk balance of a product, following a **conditional approval** based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;
- gathering **evidence through real-life use** to supplement clinical trial data;
- early and continued **involvement of all stakeholders (in particular patients, Health Technology Assessments (HTAs) and payer bodies)** in discussions on a medicine's development during the lifecycle of the product.

From a licencing perspective, this approach utilizes existing approval in stages or on the conditional approval mechanism (for medicines addressing life-threatening conditions), whereas the EMA clearly stipulates that the standards for the evaluation of benefits and risks or the requirement to demonstrate a positive benefit-risk balance to obtain a MA do not change⁴³. However, as laid out above, the calculation of RDP and SPC periods begins at the point of the initial MA grant for that product, regardless of whether this is based on a full MA or “only” a conditional MA and/or of the time period to market (and patient) access. For any earlier approval (than current) – even if it is only in a restricted patient population, on a conditional or stepwise basis – the clock of RDP and the SPC protection period begins, which as a consequence could lead to an erosion of protection periods in subsequent indications.

Impact of conditional approval and approval under exceptional circumstances on exclusivity timelines

In 2004, in order to meet in particular the legitimate expectations of patients and to take into account the increasingly rapid progress of science and therapies, the EU legislator did not only set up accelerated assessment procedures for medicinal products of major therapeutic interest, but also procedures for obtaining temporary MAs subject to certain annually reviewable conditions.⁴⁴

- The possibility of an approval under exceptional circumstances got introduced for all medicinal products⁴⁵. This allows the MA grant holder to be subject to certain conditions, so called specific obligations (SOBs). In particular, relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and additional action to be taken, as required. Such a MA may only be granted when the applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use and must be based on rarity of the condition, state of scientific knowledge, or ethical grounds.⁴⁶ Continuation of such a MA shall be linked to the annual re-assessment of the conditions mentioned above.
- In addition, the EU legislator introduced for medicinal products eligible to be approved centrally in Article 14 (8) of Regulation 726/2004 the possibility to obtain a conditional MA being subject to certain specific obligations and to be reviewed annually.⁴⁷

Amongst the currently centrally authorised medicinal products in the EU, there are 20 medicinal products that got conditional approval⁴⁸, and 30 products were approved under exceptional circumstances⁴⁹. These two concepts raise interesting questions when it comes to the lifecycle of the MA and the exclusivity rights linked to it.

Case study 2: Hypothetical substance 'A' gets submitted for conditional approval or to be approved under exceptional circumstances under adaptive pathways. Two key questions present themselves:

(1) What happens to the RDP period when a conditional MA or a MA granted under exceptional circumstances (having met the conditions set out for it) is subsequently granted a full (unconditional) MA? This clearly has no impact on the exclusivity periods that started running with the initial conditional approval or approval under exceptional circumstances as all that happened is that the validity of the MA is now unconditioned so that nor further (yearly) renewal is necessary.

(2) What happens to the RDP period if the conditions are not met (e.g. confirmatory data package is insufficient) and the conditional MA or the MA under exceptional circumstances gets revoked/suspended? Under the current legislation, the period of exclusivity rights is not impacted by a MA suspension, as it was triggered by the initial approval and therefore continues to run. As a consequence, in the case that the same applicant would be able to provide a more robust data package in the future that would warrant reinstatement of the MA at a later point of time, under the current legal framework the applicant would not be eligible to get a new RDP protection for this product, but would be constrained by the original approval period.

Impact of subsequent expansion of indications under an existing MA

In accordance with the current framework, the GMA concept encompasses all presentations of the same active substance (i.e. with the same qualitative composition) authorised to the same MA holder, which expressly includes all variations and extensions of the initially authorised product. If subsequent indications get authorised via respective Type II variations (i.e. major variations, which are not an extension, and which may have a significant impact upon the quality, safety or efficacy of the medicinal product concerned) under the initial MA, the GMA concept applies without any doubt, and by this, this new indication falls under the initial RDP period. The GMA only refers to the “initial” MA as the starting point for RDP and does not differentiate between full, conditional or exceptional MAs.

Impact of authorisation of subsequent indications under a separate and self-standing centralised MA with a different name

Once a new active substance receives centralised approval for a specific indication, a new indication can only be approved under a separate and independent centralised MA if a respective MA application is eligible for the centralised pathway in accordance with Article 3 (1) and (2) of Regulation 726/2004. This includes not only biologics, advanced therapy medicinal products and orphan drugs, but also significant therapeutic, scientific or technical innovations. In case authorisation is requested for a new indication of high unmet medical need, this could be considered as a therapeutic innovation. However, the EU Commission meanwhile considers all medicinal products with the same active substance and the same pharmaceutical form and strength to be the same “specific medicinal product” in accordance with Article 82 (1) of Regulation 726/2004⁵⁰, as laid out in its Communication on “Handling of Duplicate Marketing Authorisation Applications”⁵¹ dated October 2011. This means that a difference in therapeutic indication is no more relevant with this regard, even if it relates to an unmet

medical need. In order to justify a second MA with a different name, “objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients” must be provided and confirmed by the Commission in order to be able to get the respective MA application validated by the EMA⁵².

However, according to the EU General Court, confirming the current interpretation of the EU Commission, not only are all variations and extensions of the initially authorised product covered by the GMA of the initially authorised product, but also indications that are authorised centrally under a self-standing MA, even if they meet the innovation criteria of Article 3(2) as well as the requirements of Article 82(1) of Regulation 726/2004. An example of the nuances of MA under the central procedure and a global MA are highlighted in an ongoing litigation in *Case study 3*.

Case study 3: In the cases, *Novartis vs. European Commission* (T-472/12 and T-67/13), the issue presented to the European Courts was whether a product that has been granted a separate independent MA through the centralised procedure (Aclasta), falls under the same global marketing authorisation as a previously authorised product of the same MA holder (Zometa), as otherwise this product (Aclasta) would benefit from its own self-standing RDP. The General Court denied a self-standing independent RDP period for Aclasta in its first instance (decisions dated 15 September 2015) based on a broad interpretation of the GMA principle in Article 6(1) of Directive 2001/83/EC. Essentially, the Court argues that Aclasta could have been authorised via a variation to Zometa, that it was only due to the commercial strategy of the company that it was not, and that, therefore, the Aclasta MA has to be considered as falling in the GMA of Zometa as if it were a variation of the Zometa MA. However, Aclasta has been authorised as a full separate MA, and not as a variation or extension to Zometa. In addition, it is important to understand that even if the second authorised product would benefit from its independent RDP, it does not lead to a prolongation of the RDP for the initially authorised MA as only the indications being authorised under the second new MA would fall under this additional self-standing protection. It will be highly relevant how the ECJ will rule on this case in its 2nd instance decision. As a consequence, any important subsequent additional indication or expansion of indications would be constrained between the finite period of the initial (i.e. 10 year) RDP period.

While the outcome of Case study 3 is yet to be fully resolved, the orphan market protection provides a self-standing protection of the subsequently authorised

indications, provided that; (1) these indications are also orphan indications in accordance with Article 3 of Regulation (EC) No 141/2000 and, (2) that the self-standing protection provided by the authorisation is not undermined by (1) having a low threshold for derogations based on clinical superiority⁵³ and/or (2) what is happening on the market. With regard to the latter, in particular, the increasing so-called “cross-label” use has to be taken into consideration. In this example, where a generic medicine is authorised for uses other than those patented (and at a significantly lower price than the patented medicine), there could be circumstances in which the generic medicine is prescribed or substituted for “off-label” or “cross label” and patented uses. In this respect, innovators argue that the ability of a generic company to avoid patent infringement by using an abbreviated label on the generic product ignores the commercial reality.⁵⁴ Therefore, the prescription and use of generic products for indications that are still protected by respective indication patents or other exclusivity rights raises fundamental concerns as this could undermine existing exclusivity rights and might de-incentivise pharmaceutical companies to further develop known compounds in new therapeutic indications.⁵⁵

5. Potential solutions moving forward and scope of ongoing activities

A key enabler for the implementation of adaptive pathways is to utilize current regulatory tools without changing the current legislative landscape. To exactly find a niche for adaptive pathways within and/or around current tools such as; compassionate use, accelerated access (i.e. US accelerated approval), conditional marketing authorization, EU level PRIME and UKs Early access to medicines schemes (EAMS) designations, is an evolving process. Irrespective of the fact that with any earlier approval (than current) the clock of RDP and the SPC protection period begins earlier and that this as a consequence could lead to an erosion of protection periods

in subsequent indications, it will be important to keep current exclusivity rights as well as to find counteractions to any perceived or real blocks.

Maintaining the current status quo of exclusivity rights, under adaptive pathways is challenging under the current legal framework and EU legislation. Regulatory exclusivity rights as well as the SPC are triggered by the initial authorization – irrespective of whether this is a full MA, or a conditional MA, or a MA under exceptional circumstances. As such, according to the current interpretation of the GMA (by the Commission and the General Court), new authorisations in relation to the same medicinal product, do not benefit from a separate, self-standing protection even if they are authorised under a separate self-standing MA (such as a new indication). For regulatory exclusivities, one possible solution could be that the interpretation and application of the GMA will be limited to the initial MA and all extensions and variations thereof, and that the MA holder is allowed to obtain independent MAs in case of important innovations of the initial product. For example, where the new development fulfills the “innovation criteria” for eligibility to the centralized procedure as set out in Article 3(1) and (2) of Regulation 726/2004. This might help to facilitate the development and earlier authorisation of the product in a therapeutic indication to fulfil an unmet medical need for a limited patient population as later approved innovative indications would benefit from new protection periods. Such an option would require a much closer review of the current interpretation of the GMA and related regulations.

In addition, the current legal framework does not foresee a way of “clock stop” in case the product has to be withdrawn from the market if the conditions set out in conditional MAs or MAs under exceptional circumstances are no longer met. An adequate incentive for a future “re-authorisation” in case of new, better data is currently not

foreseen, unless the Court of Justice adopts a different interpretation of the GMA and rules in favour of a separate RDP for separate MAs of the same active substance.

Learning tools

As highlighted, there are numerous considerations still to be addressed for these new adaptive routes to be fully understood and accepted by all stakeholders, and in particular for companies to feel comfortable with suitable asset protection from an earlier market entry and patient access.

This will involve understanding the current EU legislation and findings from retrospective and ongoing case studies, assessing in more detail where the current regulatory tools such as conditional MA or MA under exceptional circumstances can be better utilized, learnings from adaptive pilot schemes, engaging across all stakeholders and utilizing public-private platforms to explore issues raised and consider how similar concepts can be applied in the global health arena.

Patents are the lifeblood of the biopharmaceutical industry, which depends heavily on IP protection and regulatory exclusivity rights to justify and support its investment in R&D. Mechanisms for earlier patient access to beneficial treatments (not just innovative), means that the traditional exclusivity periods of the 'blockbuster' generation of drugs may not be able to account for a rapid expansion of disease-specific and ever smaller sub-population targeted therapies. Overlapping exclusivity periods pose a conflict to expansion for subsequent indications within a finite exclusivity window. Such a short period of exclusivity would not give developers of new technologies sufficient time or incentives to recoup their investments in R&D. The fundamentals of IP law in the US and EU are becoming more similar. In 2007, the US and EU amalgamated their applications for orphan designation into a single

application, although each regulator continues to independently review the common application. There are however, key differences that still need to be addressed. In particular the US IP laws differ from the EU with respects to prior user rights, pre-grant examination, and post-grant review. 'Conditional licensing', a key regulatory tool in the adaptive approach, is still viewed with skepticism by industry, with some interpreting it as weakening a license that they would otherwise get.

Pilot projects and multi-stakeholder studies allow complex and often unpredictable issues to be explored with all stakeholders present. In March 2014 EMA launched a pilot project to explore how the adaptive pathways approach might work in the existing regulatory framework with real medicines in development. The report on EMAs' adaptive pathways pilots is expected later in 2016. One of the pilots key concept has focused on multi-stakeholder 'safe harbour' discussions (11 proposals have gone to in-depth stage II discussions), with sponsors receiving input on their development proposals from the regulator, HTA agencies and selected payers (and patients in some cases) - intended to facilitate open discussion without any party feeling that their interests have been impeded, or any sensitive data released precipitately.⁵⁶ While there are obvious caveats with sponsor confidentiality, as to how much detail can be gleaned here, it will provide a vital feedback mechanism for logistical aspects of the multi-stakeholder interactions, data requirements, iterative process and resources required.

Multi-stakeholder engagement

One of the other core concepts in this more flexible approach to drug development is an early cross-stakeholder dialogue of the evidence to be collected at various stages. It is vital that all stakeholders are involved in the process so that it is not driven by the same 2 or 3 players who shout the loudest. While adaptive licensing and adaptive

pathways are championed to help drive innovation and expedite patient access to beneficial treatments, such potential pitfalls highlighted here in revenue generation and IP and regulatory exclusivity right protection could conversely inhibit the diffusion of innovation to patients as sponsors and industry focus on lower risk products, away from the riskier area of unmet patient need. We are challenged to find solutions within the current frameworks across sectors to void the paradox of faster regulatory approval via adaptive approaches only for patients to be frustrated by a lack of access.

Enabling Platforms

Two key ongoing European / IMI projects are exploring aspects of the adaptive approach (ADAPT-SMART⁵⁷ and GETREAL⁵⁸). The IMI is a European public-private collaboration bringing together 32 participants for which EMA is the scientific leader, to stimulate and respond to innovation.

The ADAPT-SMART program of work covers (amongst others) aspects of the drug development pathways and patient access, decision making, resource allocation and sustainability, and the landscape of IP and regulatory exclusivity rights. The program involves all constituencies, and the results are being made publicly available.

Nevertheless, the nuances of country-to-country variation in IP and RDE legislation, behaviors, and considerations of global application mean that blanket agreement is not expected. Implementation across all EU countries would however require strenuous efforts and concessions by all, and are ironically likely be a stepwise, iterative process in itself, while maintaining the ethos of patient safety and earlier access.

Conflicts of interest:

This article represents the authors' individual opinions and may not necessarily represent the viewpoints of their employers.

Alexander Meier is an employee of Novartis Pharma AG (CH).

John Kung is an employee of Novartis Pharmaceuticals Corporation (USA).

Richard Barker is chairman of the UK Precision Medicine Catapult and a non-executive board member of Celgene: CASMI is a recipient of Wellcome Trust.

David Brindley is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK) and IP Asset Ventures Ltd. (Oxford, Oxfordshire, UK), companies that among other services provide cell therapy biomanufacturing, regulatory, and financial advice to pharmaceutical clients. Brindley also is subject to the CFA Institute's codes, standards, and guidelines, so he must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation. Additionally, at time of publication, Brindley and the organizations with which he is affiliated may or may not have agreed and/ or pending funding commitments from the organizations named herein.

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Figure Legends

Figure 1 The regulatory data exclusivity ("8+2+1") formula for new drugs approved either through the centralized procedure or the mutual recognition procedure, the patent duration, and orphan product market exclusivity periods.

Orphan product exclusivity periods run parallel with regulatory data protection periods

Figure 2 The market exclusivity periods for orphan products. These are not governed by the same exclusivity periods as non-orphan products under the centralized procedure

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- ³ *European Medicines Agency*, Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004, of 5 December 2006 (EMA/509951/2006).
- ⁴ Tufts Center for the Study of Drug Development (CSDD), 2014. Cost to Develop and Win Marketing Approval for a New Drug Is USD 2.6 Billion.
- ⁵ See EFPIA, Intellectual Property and Pharmaceuticals, 13 June 2008, p. 4 f.
- ⁶ Arshad et al., Open Access Could Transform Drug Discovery: A Case Study of JQ1, *Expert Opinion on Drug Discovery*, 2016, Vol. 11, No. 3, 321-332.
- ⁷ Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, OJ L 182 of 2.7.1992, p. 1, meanwhile replaced by Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152 of 16.6.2009, p. 1.
- ⁸ TRIPS is an international agreement administered by the World Trade Organization (WTO) that sets down minimum standards for many forms of intellectual property (IP) regulations in WTO Member States. It was concluded at the end of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) in 1994.
- ⁹ Art. 39 TRIPS provides protection of undisclosed clinical/scientific data submitted to Health authorities for getting a MA, and stipulates in its paragraph 3: "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."
- ¹⁰ See for the EU Article 10 (1) of Directive 2001/83/EC and Article 8(1) of Regulation 141/2000.
- ¹¹ IFPMA, Data Exclusivity: Encouraging Development of New Medicines, July 2011.
- ¹² The consequence is that the second applicant has to generate its own data as he cannot refer to the data in the dossier of the reference medicinal product being protected by RDP, provided that from an ethical perspective it is acceptable to repeat comparable clinical trials.
- ¹³ See e.g. Recital 4 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L of 27.12.2006, p. 1.
- ¹⁴ These are in particular the European Patent Convention (EPC) of 1973, the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), the Patent Law Treaty (PLT) and the London Agreement.
- ¹⁵ The EPO was established by the European Patent Convention, and has the legal status of a public international organisation. The EPO is not an institution of the European Union or of the Council of Europe.
- ¹⁶ Regulation (EU) No. 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection, OJ L 361 of 31.12.2012, p. 1, and Council Regulation (EU) No 1260/2012 of 17 December 2012 implementing

enhanced cooperation in the area of the creation of unitary patent protection with regard to the applicable translation arrangements, OJ L 361 of 31.12.2012, p. 89.

¹⁷ See <http://www.epo.org/law-practice/unitary/unitary-patent.html>.

¹⁸ Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152 of 16.6.2009, p. 1.

¹⁹ 'Basic patent' means a patent which protects a product as such, a process to obtain a product or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate, Article 1 (c) of Regulation 469/2012.

²⁰ See Recitals 4-8 of Regulation (EC) No 469/2009.

²¹ Recital 9 and Article 13 (1) and (2) of Regulation (EC) No 469/2009.

²² See Articles 19 and 20 of Regulation (EC) No 469/2009.

²³ Nationally approved are not only those medicinal products approved via national procedure, but also those being approved via decentralised or mutual recognition procedure.

²⁴ These are listed in Article 8(3) and the Annex to Directive 2001/83.

²⁵ The justification of abridged procedures is that additional tests and trials would not contribute to ensuring public health to the extent that safety and efficacy has already been proven in relation to the same substance [2]. Furthermore, the abridged procedures facilitate the coming to the market of cheaper products which also contributes to public health in the EU.

²⁶ See also European Commission, Notice to Applicants, Volume 2A, Procedures for marketing authorization, Chapter 1: Marketing Authorisation (Revision 5), July 2015.

²⁷ See Article 10 (1) of Directive 2001/83 and Article 14 (11) of Regulation 726/2004.

²⁸ In addition to that, but less relevant, additional forms of RDP are provided for in Article 10(5) and 74a of Directive 2001/83. Article 10(5) provides for a one year period of data exclusivity for significant preclinical or clinical studies which are carried out in relation to the development and authorisation of a new indication for a well-established substance. Article 74a offers another one year of data exclusivity for significant preclinical tests and clinical trials which have been conducted for a change in the classification of a medicinal product whether it is or not subject to a medical prescription.

²⁹ .S. Code, Title 21, § 355(c)(3)(E); and Sections 7002(a)(7)(A) and 7002(a)(7)(C) of the Affordable Care Act, adding sections 351(k)(7)(A) and 351(k)(7)(C) of the Public Health Service Act.

³⁰ Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999, OJ L 18 of 22.1.2000, p. 1.

³¹ For some applications, including abridged applications, the agreement of such PIP is not required while it is also possible to obtain a waiver or deferral of the PIP obligation pursuant to Articles 9 ff of Regulation 1901/2006.

³² See Article 8(1) of Regulation 1901/2006.

³³ By this, the duration of the SPC can effectively be extended to a maximum of 5.5 years.

³⁴ Article 36 (4) of Regulation 1901/2006.

³⁵ The legislature introduced the notion of a global marketing authorisation ("GMA") through Directive 27/2004/EC by amending Article 6(1) of Directive 2001/83 to include a new subparagraph.

³⁶ See www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000392.jsp&.

³⁷ Article 14(7) of Regulation (EC) No 726/2004

³⁸ Article 14(8) of Regulation (EC) No. 726/2004 and Article 22 of Directive 2001/83/EC.

³⁹ Articles 9.4 c, c, ca, cb, cc of Regulation (EC) No 726/2004 and Article 21a of Directive 2001/83/EC.

⁴⁰ Article 83 of Regulation (EC) No 726/2004. In this context, the term ‘compassionate use’ is defined in Article 83 (1) of Regulation (EC) No 726/2004 as “making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be lifethreatening, and who cannot be treated satisfactorily by an authorised medicinal product”.

⁴¹ Article 5(1) of Directive 2001/83/EC.

⁴² See EMA-homepage

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce.

⁴³ See EMA-homepage

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce.

⁴⁴ See Recital 33 of Regulation 726/2004.

⁴⁵ Article 22 of Directive 2001/83/EC and its Annex I, Part II.6, and Article 14 (8) of Regulation 726/2004.

⁴⁶ These grounds are set out in Annex I of Directive 2001/83/EC.

⁴⁷ The provisions for granting such conditional MAs are laid down in Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, OJ L 92 of 30.03.2006, p. 6.

⁴⁸ Adcetris, Arepanrix, Arzerra, Blincyto, Bosulif, Caprelsa, Cometriq, Darzalex, Delytba, Erivedge, Fampyra, Holoclar, Humenza, Pandemic Influenza vaccine H5N1 MedImmune, Pixuvri, Sirturo, Tagrisso, Translarna, Xalkori and Zykadia (manual research on EMA website, performed on 18 June 2016).

⁴⁹ Adjupanix, Atriance, ATryn, Ceplene, Daronrix, Defitelio, Elaprase, Evoltra, Firdapse, Foclivia, Glybera, Ilaris, Imvanex, Increlex, Kolbam, Lojuxta, Naglazyme, Obizur, Onsenal, Orphacol, Pandemic Influenza Vaccine H5N1 Baster AG, Pumarix, Raxone, Rilonacep Regeneron, Scenesse, Strensiq, Vedrop, Vyndaqel, Xagrid, Xigris (manual research on EMA website, performed on 18 June 2016).

⁵⁰ Article 82(1) of Regulation 726/2004 stipulates: “Only one authorisation may be granted to an applicant for a specific medicinal product. However, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons.”

⁵¹ European Commission, Handling of Duplicate Marketing Authorisation Applications, SANCO/D3/RSR/iv(2011)ddg1.d3. 1137738, Update 1 (October 2011).

⁵² EMA, Procedural announcements – CHMP meeting 14-17 November 2011, dated 17 November 2011 (EMA/CHMP/877159/2011).

⁵³ Article 8(3)(b) of Orphan Regulation allows by way of derogation from the OME of a previously approved orphan product that a MA may be granted, for the same therapeutic indication, to a similar medicinal product if “the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.”

⁵⁴ [Http://united-kingdom.taylorwessing.com/synapse/ti_infringement2nduse.html](http://united-kingdom.taylorwessing.com/synapse/ti_infringement2nduse.html).

⁵⁵ See EFPIA, New Indications & Cross-Label Dispensing, 11 November 2015.

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